3. Clinical protocol.

3.1 Overall design. The protocol is designed to determine the safety/toxicity and biologic efficacy of direct administration of the Ad_{GV}VEGF121.10 vector to the myocardium of individuals with diffuse coronary artery disease via minimally invasive surgery. At the conclusion of the study, the following objectives will be met.

1. To determine the safety/toxicity of direct administration of the vector Ad_{GV}VEGF121.10 to the ischemic myocardium.

2. To demonstrate whether direct administration of Ad_{GV}VEGF121.10 to the myocardium will induce growth of collateral blood vessels, improve coronary blood flow and improve cardiac function in the region of ischemia.

The proposed clinical protocol is a safety/toxicity study that will determine the safety of administering Ad_{GV}VEGF121.10 to the myocardium of individuals with diffuse coronary artery disease via minimally invasive surgery. This protocol will use a dose [$4x10^9$ particle units (pu)] that has been used in humans and determined to be safe under our current protocol (BB-IND , RAC #9711-211; The New York Hospital-Cornell Medical Center Insitiutional Review Board #0794-894). The present protocol and protocol 0794-894 are essentially identical except that the present protocol uses minimally invasive surgery to administer the vector as the sole therapy, whereas protocol 0794-894 combines administration of the vector with coronary artery bypass graft surgery (CABG).

The Ad_{GV}VEGF121.10 vector will be administered directly to the myocardium during the minimally invasive cardiac surgical procedure using a insulin syringe with a 28 gauge needle (Appendix A3.2, A3.3). For each individual, the total dose of vector will be divided into 10, 100 µl aliquots, with each aliquot administered to a site separated by 1.5 - 2.0 cm. Although the region of administration of the vector will vary from patient to patient, the method of administration of the vector, the number of sites of administration, the volume of each administration, and the total area of administration, will be similar for all patients in each group. The minimally invasive surgical procedure will be carried out solely for the purpose of administration of the vector. As discussed below, individuals in this group represent individuals with clinically significant coronary artery disease that, in the opinion of the individual's cardiologist, are not optimal candidates for CABG or percutaneous transluminal coronary angioplasty (PTCA).